and in the original claims of the application. In particular, support for the newly proposed claims appears in the present application at page 5, lines 5-14, page 8, lines 8-15 and lines 21-24, page 14, lines 2-7, and page 20, lines 6-13.

As an initial matter, Applicants respectfully request that the finality of the rejection be withdrawn. Specifically, it is submitted that the final rejection was premature in that the claims have only been examined on the merits *once*. By way of history, a first office action issued by the PTO on November 23, 2001 (paper no. 8), indicated that claims 17-21 were merely objected to under 37 CFR 1.75(c) as being in improper multiple dependent form, and as reciting a dependency to a non-elected invention. The Office Action expressly indicated that these claims were therefore *not examined on the merits*. Applicants subsequently filed an Amendment on February 25, 2002 (paper no. 9), to present the claims in a format suitable for examination. In particular, claims 17-21 were cancelled and rewritten as new claims 22-29. These claims have now been *substantively examined only once*, however, the status of the rejection is indicated as being *final*. It is submitted that the final status of the rejection is clearly improper. Reconsideration and withdrawal of the finality of the rejection are thus requested.

If the finality of the rejection is maintained, however, it is provisionally submitted that the within amendments may still be properly entered at this time, i.e. after final rejection, pursuant to 37 CFR §1.116, because the amendments do not raise any new issues or require a new search, and they reduce issues for appeal. Indeed, it is believed that the within amendments place the application in condition for allowance. Accordingly, entry of the within amendments is earnestly solicited at this time.

Applicants appreciate the indication of allowable subject matter, i.e., that claims 25 and 29 would be allowable if rewritten in independent form and amended to overcome the rejection under 35 USC §112, second paragraph. It is noted, however, that no rejections under 35 USC §112, second paragraph have been set forth in the Office Action.

Claims 22-24 and 26-28 are rejected under 35 USC§112, first paragraph. As grounds for the rejection, it is alleged that the noted claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application as filed. The Office Action goes on to expressly acknowledge that the specification is enabling for SEQ ID NO:1 and the modified nucleic acid sequence of *Saccharomyces cerevise* FRE1 gene. However, the position is taken that the specification allegedly does not reasonably provide enablement for the scope of possible nucleic acid sequences claimed for use in plants.

The rejection is traversed.

Applicants respectfully submit that the claims of the application are amply supported by the specification, and that the present application fully satisfies the requirements of Section 112, including the written description and enablement requirements of 35 USC §112, first paragraph.

The Office Action alleges that the specification does not provide any other example genes which would require modification other than the yeast FRE1 gene for expression in tobacco.

Attention is directed to the present application at page 3, line 22, to page 4, line 12, where Applicants describe certain instances where incomplete transcription has been achieved, e.g., where a gene of another species has been transformed into a higher plant by introducing a gene of another organism species. It is noted that although transformation of the higher plant has been shown, expression was low to non-existent.

The present invention provides novel methodology for gene modification to improve the expression of a foreign gene. The underlying principle of Applicants' invention is based on the difference among the transcriptional system of the plant and that of the donor species. It is respectfully submitted that a person skilled in the art could readily apply Applicants' novel methodology for introducing any foreign gene into any plant species. In that way, Applicants'

disclosure (together with the level of knowledge and skill in the art) is enabling well beyond the case where the yeast FRE1 gene is introduced into tobacco. Again, the reason being, that the underlying principle is based on the difference among the transcriptional system of the plant and that of the donor species, and because there are certain other studies which were performed before the present application was filed which are duly reported by Applicants in the specification (as noted above) and which contribute to the level of knowledge and skill in the art.

Moreover, Applicants surprisingly discovered that the GT rich region located upstream of the polyadenylation signal sequence (AATAAA like sequence) defines the addition of poly(A) of mRNA (polyadenylation). In polyadenylation, immature mRNA is digested in the position of 10 to 30bp downstream of the polyadenylation signal sequence, and then the poly(A) sequence is added at the end of the RNA by an action of poly(A) polymerase. Additionally, if a transgene contains the GT rich region and following polyadenylation signal sequence in the middle, the expressed mRNA is short and does not have enough length for coding the full amino acid sequence in the plant.

Applicants' invention resides in a nucleic acid having a base sequence modified by features (A) and (B), for eliminating sequences relating to the polyadenylation of mRNA. In each of the noted features, modifications are carried out such that the amino acid sequence of the gene remains unchanged (see independent claims 30). Features (A) and (B) are defined as follows:

(A) GT rich regions are eliminated, specifically 8 or more consecutive bases of G or T, and

(B) sequences encoded by AATAAA, NATAAA, ANTAAA, AANAAA, AATNAA, AATANA, and AATAAN are eliminated.

Further, Applicants' invention provides novel methodology for modifying the base sequence of a transgene which results in significantly enhanced expression of the gene. Applicants' invention is based on the fact that the GT rich region of the base sequence defines polyadenylation in plants.

Thus, Applicants' invention is not confined to merely the nucleic acid structure specific to the FRE1 gene, nor to the feature of the transcriptional system of tobacco. Applicants' invention and its underlying principle are based on the difference between the transcriptional system of plant and that of the donor species. As such, the full scope of the claims are enabled.

Based upon the present application and the level of skill and knowledge in the art, one could readily apply Applicants' principle to introduce any foreign gene into any plant species. By way of illustration, the GT rich region would first be identified by searching for the 8 or more consecutive bases of G or T in the base sequence of the gene which would be introduced into the plant. A nucleotide sequence would then be designed for eliminating the GT rich region, in particular, by changing the codon usage in the GT rich region. As is known, an amino acid is coded by a triplet code, that is, one amino acid has 3 bases per codon. A point mutation in a third codon position is phenotypically silent. Therefore, one skilled in the art could utilize Applicants' enabling disclosure to design a modified nucleotide sequence by mutating the third codon position without changing the amino acid sequence. Following that, one could synthesize the designed base sequence by the method described in the prior art or by the method described in the present application. (See the present application at page 9, line 19, to page 10, line 1, page 12, line 17 to page 14, line 1, for the related discussion of the method of synthesizing a long length base sequence.)

The Office Action also asserts that it is allegedly not clear from making at least one of the claimed modifications to any possible nucleic acids, absent further characterization of the expressed protein in plants, that one of skill in the art would be able to use any such nucleic acid sequence having the function of expression in any plant. The Office Action goes on to state, that while it is known that many amino acid substitutions are generally possible in any given protein without changing the protein's function, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited.

In order to address that aspect of the rejection, the claims as amended recite the additional feature --without altering the amino acid sequence--. It is submitted that one skilled in the art could readily apply Applicants' disclosure and design the modified nucleotide sequence by mutating the third codon position without changing the amino acid sequence. For example, SEQ ID NO:1 is the modified base sequence of FRE1 gene without changing the amino acid sequence.

Reconsideration and withdrawal of the rejections are requested.

It is believed the application is in condition for immediate allowance, which action is earnestly solicited.

Respectfully submitted,

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